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ORIGINAL ARTICLE

Effects of Androgens on the Thickness of Retinal Layers in Transgender Men and in Women with Polycystic Ovarian Syndrome

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Abstract

Purpose: This study aimed to evaluate the relationship between androgens and the retinal thickness by comparing the macular thickness (MT), retinal nerve fiber layer (RNFL), and ganglion cell complex (GCC) thickness of female-to-male transgender men (TGM), women with polycystic ovary syndrome (PCOS), and cisgender women (CW).

Methods: Thirty-four eyes of 34 TGM, 34 eyes of 34 women with PCOS, and 45 eyes of 45 CW were evaluated by optical coherence tomography. One-way analysis of variance and body mass index (BMI)-adjusted one-way analysis of covariance were conducted to test the differences between groups for statistical evaluation.

Results: The parafoveal MT in TGM was significantly higher than women with PCOS and CW ($p < 0.001$ and $p = 0.022$, respectively). After adjusting for BMI, the perifoveal MT in TGM was significantly higher than women with PCOS and CW ($p = 0.041$ and $p = 0.021$, respectively). The nasal RNFL thickness in TGM was significantly higher than women with PCOS and CW ($p = 0.021$ and $p = 0.009$, respectively). The means of average and inferior RNFL, fovea, and the mean of all GCC values were higher in the TGM group than women with PCOS and CW, but these results were not statistically significant.

Conclusions: In this study, there was a significant difference between the TGM group and the CW group for the thickness of the nasal RNFL and parafoveal and perifoveal macular area. Androgens may have the potential to increase retinal thickness in TGM; however, there is a need for validation in larger study groups. Clinical Trial Registration Number: HNEAH-KAEK 2021/4.

Keywords: androgen; polycystic ovarian syndrome; retina; retinal nerve fiber layer; testosterone; transgender men

Introduction

Eye diseases exhibit different physiological and pathological characteristics in men and women, drawing attention to the effects of sex hormones on the eye.[1] Further leading researchers to study these effects is the fact that gonadal hormone receptors have been identified in many regions of the eye, including the conjunctiva, lacrimal gland, cornea, iris, ciliary body, and retina.[2,3]

Many studies of the effects of sex hormones on women have focused on the effects of estrogen. Studies conducted in premenopausal and postmenopausal women have reported the neuroprotective effects of estrogen, such as reducing the intraocular pressure (IOP) and increasing the ocular blood flow.[4,5] However, it has been suggested that testosterone works as an estrogen antagonist.[6]

Studies analyzing the effects of testosterone on women's eyes are limited, and mostly focus on individuals with polycystic ovary syndrome (PCOS). PCOS is characterized by ovulatory dysfunction, an irregular menstrual cycle, and hyperandrogenism. In animal studies, high levels of nerve growth factor were found in cases of animals with PCOS.[7] In addition, in clinical

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studies, an increase in IOP and retinal nerve fiber layer (RNFL) thickness was reported in women with PCOS.[8,9] The neuroprotective effects of testosterone on the nervous system have also been demonstrated through the regeneration and, thus, healing of neurons and glia.[10–12]

The transition for transgender men (TGM) can include exogenous testosterone use, breast excision, oophorectomy, and hysterectomy. However, there are few studies reporting on the ocular effects of exogenous testosterone in TGM. A recent study reported that TGM using supraphysiological doses of testosterone have a greater macula, RNFL, and ganglion cell complex (GCC) thickness, and a higher IOP than do cisgender women (CW).[13]

As such, this study aimed to evaluate the effects of androgens on the retinal thickness of female-to-male TGM who have been using testosterone for at least 1 year and that of women with PCOS, and to compare the results with those of CW.

Materials and Methods

This prospective and cross-sectional study was carried out in accordance with the tenets of the Declaration of Helsinki and approved by the Research Protocol and Ethics Committee of Haydarpasa Numune Training and Research Hospital (HNEAH-KAEK 2021/4). Informed written consent for data collection was obtained from all participants after an explanation of the nature of the study.

In total, 113 subjects were enrolled in this study. Specifically, this study included 34 eyes of 34 TGM (Group 1), 34 eyes of 34 women with PCOS (Group 2), and 45 eyes of CW (Group 3). Only the right eyes of all subjects were included in this study.

A detailed systemic history was taken from all subjects, and full ophthalmological examinations were performed. In all groups, individuals with a history of systemic disease (i.e., endocrine diseases, collagen vascular disease, diabetes mellitus, hypertension, and cardiovascular diseases) and those with any ocular diseases were excluded from the study. None of the cases in any of the groups had a history of any ocular disease, and refractive errors were not greater than ± 3 diopters in terms of the spherical equivalent. The axial length of each of the studied eyes was between 20 and 25 mm. The best-corrected visual acuity was over 8/10 according to the Snellen chart (decimal) in all subjects.

A total of 34 eyes of 34 individuals between the ages of 18 and 45 years who had been using testosterone for at least 1 year at the time of the study to transition from female-to-male constituted Group 1. All the TGM subjects were evaluated before hysterectomy and bilateral salpingo-oophorectomy. All cases had normal menstrual cycles before testosterone use, and the ovarian sizes were within normal limits. Of the 34 cases, 6 were using a vial of Nebido (testosterone undecanoate, Bayer, Germany; 1000 mg/3 months), whereas 28 were using Sustanon (testosterone propionate 30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 69 mg, or testosterone decanoate 100 mg, Eczacıbaşı, Turkey; 250 mg/month).

Group 2 included 34 eyes of 34 women with PCOS. These women were diagnosed with PCOS according to the Rotterdam criteria in the Obstetrics and Gynecology Clinic. These criteria were reported as clinical or laboratory findings of hyperandrogenism, ovulatory dysfunction, and/or polycystic ovarian morphology (i.e., the ovarian volume being $>10\,cm^3$ or the number of antral follicles being >12). Women with newly diagnosed PCOS who were referred to the Obstetrics and Gynecology Clinic outpatient clinic and who had never received hormone therapy previously were included in the study.

The control group (i.e., Group 3) included 45 eyes of 45 CW. Group 3 was formed in such a way as to age-match with the study groups. None of the participants in Group 3 were receiving any hormone treatments and/or supplements or aromatase inhibitors, and none were pregnant or breastfeeding at the time of data collection. Women with irregular menstrual cycles, irregular oligoanovulatory cycles, or hyperandrogenism with clinical findings were not included in Group 3. All measurements were taken in the follicular phase of the last menstrual cycle in all CW.

The serum estradiol and free testosterone levels of the participants in Groups 1 and 2 were measured. Testosterone levels could not be measured in Group 3. However, all CW were selected amoung women without clinical hyperandrogenemia; the presence of clinical hyperandrogenemia was determined by physical examination, the absence of acne and seborrhea, and a Ferriman–Gallwey score of 7 or below.[14]

Ophthalmological evaluation

A full ophthalmological examination was performed on each participant. The data collected included their medical history, best-corrected visual acuity, detailed fundus examination result, IOP measurement using Goldmann applanation tonometry, and central corneal

thickness (CCT) measurement. The macular thickness (MT), RNFL, and GCC measurements were taken using Fourier-domain optical coherence tomography (RTVue-100, Optovue, Fremont, CA). Measurements or artifacts with a low signal strength (< 50) that did not focus on the fovea or optic disc center were not evaluated.

To obtain MT measurements, nine sectoral thickness subfields in three concentric circles were mapped, with diameters of 1, 3, and 6 mm (Fig. 1a). The foveal, parafoveal, and perifoveal thicknesses were also evaluated. The RNFL thickness was measured using 13 concentric ring scans of 1.3–4.9 mm in diameter, centered on the optical disc. The average, superior, inferior, temporal, and nasal RNFL measurements were evaluated (Fig. 1b). Last, GCC thickness was measured in 1 horizontal line with a scan length of 7 mm and in 15 vertical lines with a scan length of 7 mm; the average, superior, and inferior GCC measurements were evaluated.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 22 (IBM® Corp, New York, NY). The results are expressed as mean ± standard deviation. The suitability of the parameters to the normal distribution was evaluated with the Kolmogorov–Smirnov and Shapiro–Wilk tests. If the data were normally distributed, parametric statistical tests were used; otherwise, nonparametric tests were used.

The differences between all study groups in terms of age, body mass index (BMI), IOP, CCT, and visual acuity measurements were determined using a one-way analysis of variance (ANOVA).

An ANOVA and a one-way analysis of covariance, with adjustments for BMI, were performed for the differences between all study groups in terms of the MT, RNFL, and GCC measurements. A p-value of < 0.05 was considered statistically significant.

Results

The characteristics of the participants, including the mean values of age, BMI, cup-to-disc ratio, IOP, and CCT, are shown in Table 1. There was a significant difference between the TGM group (Group 1) and CW group (Group 3) in relation to BMI ($p = 0.002$). The duration of testosterone use in the TGM group was 27.41 ± 9.53 months (minimum 12 months; maximum 60 months). In Group 1, the mean serum estradiol level was 74.44 ± 61.96 pg/mL and the free testosterone level was 19.41 ± 29.89 pg/mL. In the PCOS group (Group 3), the mean serum estradiol level was 41.00 ± 23.10 pg/mL and the free testosterone level was 3.29 ± 1.44 pg/mL.

The mean RNFL, GCC, and MT values of Groups 1, 2, and 3 are shown in Table 2.

The parafoveal MT in Group 1 was significantly higher than that in Groups 2 and 3 ($p < 0.001$ and $p = 0.022$, respectively). After adjusting for BMI, the parafoveal MT in Group 1 was significantly higher than that in Groups 2 and 3 ($p < 0.001$ and $p = 0.002$, respectively). Similarly, after adjusting for BMI, the perifoveal MT in Group 1 was significantly higher than that in Groups 2 and 3 ($p = 0.021$ and $p = 0.041$, respectively). The nasal RNFL thickness was also significantly higher in Group 1 than it was in Groups 2 and 3 ($p = 0.021$ and $p = 0.009$, respectively). After adjusting for BMI, the nasal RNFL thickness in Group 1 was significantly higher than it was in Groups 2 and 3 ($p = 0.015$ and $p = 0.009$, respectively). Last the means of the average and inferior RNFL, fovea, and all GCC values were higher in Group 1 than they were in Groups 2 and 3, but these results were not statistically significant.

Discussion

In this study, we aimed to evaluate the effects of androgens on retinal thickness of female-to-male TGM who had been using testosterone for at least 1 year and in women with PCOS, and to compare the results with those of a control group of CW. Although we observed a greater thickness in almost all retina parameters in TGM, only the parafoveal MT and nasal RNFL thicknesses exhibited statistical significance. In addition, the perifoveal macular area was significantly higher in the TGM group, after an adjustment for BMI was made during statistical analysis.

Past studies on the effects of testosterone on the retina are limited, and the few that have been done have focused on women with PCOS who have high androgen levels. Some studies have reported an increased RNFL thickness in women with PCOS, and it was assumed that this might be due to the growth factor that has been detected in individuals with PCOS.[8] In our study, although the mean RNFL thickness in the PCOS group was higher than that in the CW group in all quadrants, there was no statistically significant difference between the groups.

Some studies have reported an increased MT in women with PCOS, and it has been suggested that this increase in thickness may be related to the metabolic

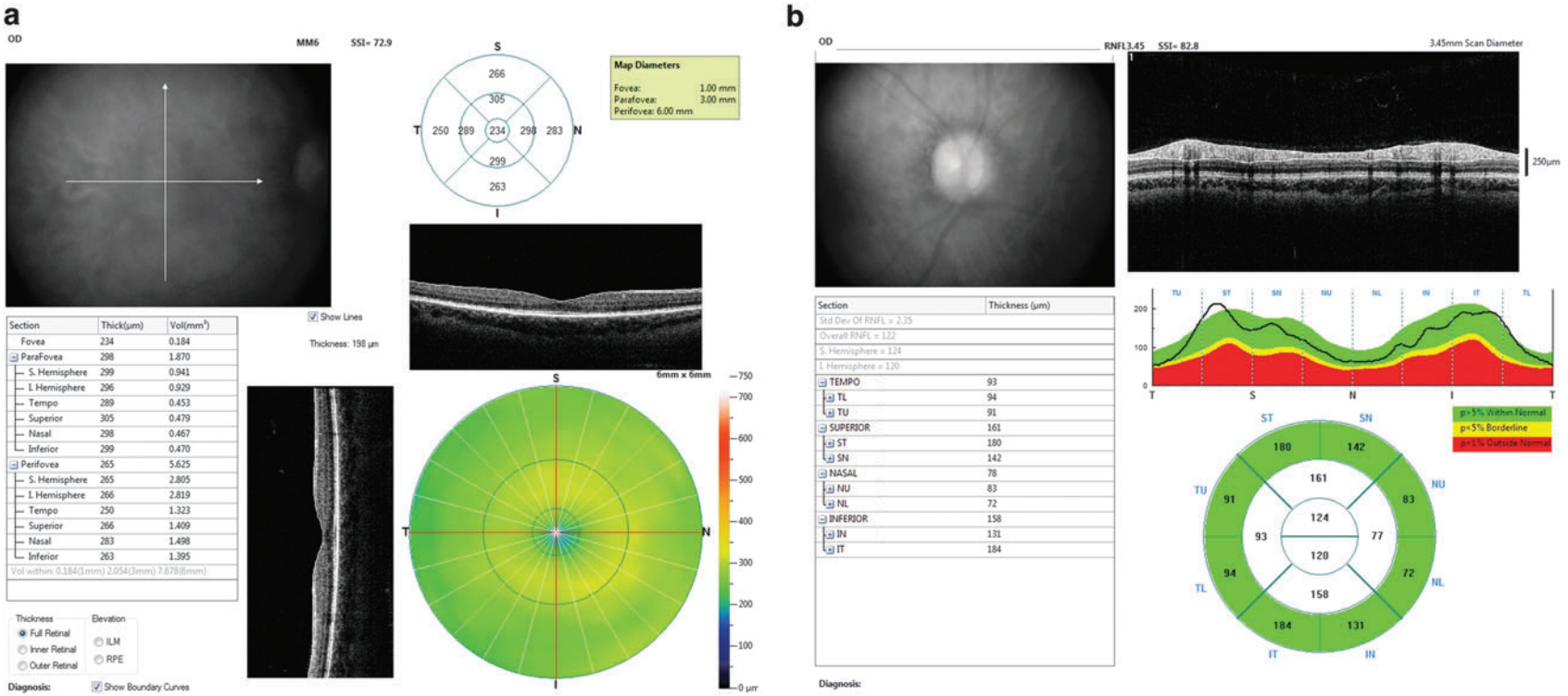

FIG. 1. **(a)** Measuring macula thickness in three concentric circles of diameters 1, 3, and 6 mm. **(b)** Measuring retinal nerve fiber layer thickness using 13 concentric ring scans 1.3–4.9 mm in diameter centered on the optic disc.

Table 1. Mean Values of Age, Body Mass Index, Refraction, Vision Level, Intraocular Pressure, Cup to Disc Ratio, and Central Corneal Thickness in Transgender Men, Women with Polycystic Ovarian Syndrome, and Cisgender Women

	TGM (Group 1) (n=34)	PCOS (Group 2) (n=34)	CW (Group 1) (n=45)	p[a]
Age (years)	27.41 ± 5.09	25.37 ± 5.11	26.64 ± 4.96	0.239
BMI (kg/m^2)	24.88 ± 4.25	23.49 ± 4.39	21.9 ± 2.6	**0.003***
				1–3
				0.002*
Refraction (diopters)	−0.28 ± 0.97	−0.54 ± 0.72	−0.4 ± 0.69	0.398
Vision level (logmar)	0.0015 ± 0.008	0.00 ± 0.00	0.00 ± 0.00	0.097
IOP (mmHg)	16.03 ± 2.96	15.71 ± 2.65	15.29 ± 2.38	0.462
C/D ratio	0.15 ± 0.07	0.14 ± 0.07	0.14 ± 0.07	0.668
CCT (μm)	552.71 ± 28.72	553.83 ± 32.27	550.31 ± 30.92	0.871

Bold denotes statistically significant.
BMI, body mass index; C/D, cup to disc; CCT, central corneal thickness; CW, cisgender women; IOP, intraocular pressure; PCOS, polycystic ovarian syndrome; TGM, transgender men.
*$p < 0.05$.
[a]One-way analysis of variance.

syndrome seen in women with PCOS.[9] Contrary to these studies, a recent study found the retinal thickness to be thinner in women with PCOS than it is in CW, suggesting that this may be due to the neurodegeneration that occurs as a result of insulin resistance or subclinical retinal inflammation.[15] In our study, the MT in the parafoveal area in women with PCOS was significantly thinner than the same area in TGM individuals; however, there was no difference between women with PCOS and the CW.

Rothman et al.[16] reported the mean free testosterone in premenopausal women as 1.8 ± 0.15 pg/mL. In our

Table 2. Comparison of Retinal Nerve Fiber Layer, Ganglion Cell Complex, and Macular Thickness Values in Transgender Men, Women with Polycystic Ovarian Syndrome, and Cisgender Women

	TGM (Group 1)	PCOS (Group 2)	CW (Group 3)	p[a]	p[b]
RNFL					
Average	110.47 ± 9.13	108.94 ± 8.36	107.04 ± 9.59	0.251	0.218
Temporal	84.18 ± 10.57	84.06 ± 9.5	83.98 ± 11.65	0.997	0.981
Superior	135.56 ± 15.31	136.26 ± 15.38	133.007 ± 14.68	0.606	0.665
Nasal	85.03 ± 12.53	78.94 ± 9.74	78.53 ± 9.74	**0.019***	**0.016***
				1–2 **0.021***	1–2
				1–3 **0.009***	**0.015***
					1–3
					0.009*
Inferior	137.53 ± 16.00	134.49 ± 17.25	132.4 ± 17.17	0.411	0.322
GCC					
Average	100.29 ± 6.47	98.54 ± 7.42	98.4 ± 6.53	0.422	0.207
Superior	99.38 ± 6.92	97.64 ± 7.35	98.07 ± 6.11	0.535	0.285
Inferior	101.21 ± 6.59	99.45 ± 7.91	98.96 ± 7.13	0.374	0.226
MT					
Fovea (1 mm)	241.32 ± 23.82	234.51 ± 15.84	236.58 ± 15.04	0.290	0.273
Parafovea (3 mm)	321.44 ± 12.89	310.74 ± 11.47	314.86 ± 12.53	**0.002***	**<0.001***
				1–2	1–2
				<0.001*	**<0.001***
				1–3 **0.022***	1–3
					0.002*
Perifovea (6 mm)	284.29 ± 12.35	278.51 ± 9.01	280.42 ± 11.51	0.091	**0.046***
					1–2
					0.041*
					1–3
					0.021*

Bold denotes statistically significant.
GCC, ganglion cell complex; MT, macular thickness; RNFL, retinal nerve fiber layer.
*$p < 0.05$.
[a]One-way analysis of variance.
[b]Body mass index adjusted one-way analysis of covariance.

study, the free testosterone level in the PCOS group was 3.29 ± 1.44 pg/mL, whereas that in the TGM group was 19.41 ± 29.89 pg/mL. In addition, although there was no statistical difference between the mean age of the three groups in our study, the mean age of the participants in the PCOS group was the lowest. The PCOS group may have visited the Gynecology and Obstetrics Clinic at an earlier age due to symptoms of menstruation irregularity and hyperandrogenism. Exposure times and lower androgen levels than TGM group of these individuals may explain why the effect of androgens in our PCOS group was different from that of the TGM group.

It has been reported that testosterone has a neuroprotective effect by regenerating and, thus, healing neurons and glia, and by increasing the axonal caliber and myelin sheath thickness.[10–12] Testosterone can exert its neuroprotective effect either directly or through conversion to estrogen.[17] In addition, a recent study performed by the authors of this study reported that the macular, RNFL, and GCC thicknesses were higher in TGM than in CW. In some areas, these thickness levels were even higher in TGM than in the cisgender male control group. In addition, there was a positive correlation between the testosterone and RNFL thickness.[13]

The effects of testosterone on the retinal layers can also be evaluated through studies examining the differences between the genders. Many such studies have reported that the MT is higher in men than it is in women.[18–20] These results are consistent with the fact that the mean MT of our TGM group was higher in all three ring areas compared with the CW group. However, the PCOS group did not exhibit a similar finding in our study.

The RNFL thickness, in contrast, has been found to be significantly higher in women than in men in many studies.[21,22] However, some studies have found the average RNFL to be similar in men and women.[23] In our study, the RNFL value was significantly thicker in the nasal quadrant in the TGM group, a finding that may or may not be significant. Because the standard deviation value in the TGM group was higher in this area than it was in the other groups, this significance must be carefully evaluated. However, the mean RNFL and GCC values were higher in almost all quadrants in the TGM group than they were in the other two groups.

The mean RNFL and GCC values of the PCOS group were also higher than those in the CW group. These findings may provide evidence of the neuroprotective and hypertrophic effects of exogenous testosterone use and endogenous testosterone elevation. However, other studies have presented evidence against the neuroprotective effects of testosterone; for example, testosterone did not provide neuroprotection against the glutamate-induced or methamphetamine-induced neurotoxicity of the dopaminergic system in mouse experiments.[24,25]

Moreover, a study investigating hormone receptors in the retina showed that although estrodiol receptors in the retina can be detected in young women, they are absent in men and in women who have entered menopause.[26] Another study reported that number of androgen receptors is higher in the brains of male mice.[27] It has also been reported that androgen receptors in the brain can be controlled by serum estrogen and androgen levels.[28] We did not find any evidence in the literature of the difference between the genders with regard to retinal androgen receptors. However, due to optic nerve and ganglion cells, which are extensions of the central nervous system, it can be assumed that exogenous androgen use and high endogenous androgen levels may cause a change in the number of hormone receptors in the retina. However, this needs to be supported by further studies.

The effects of androgens on the retina can also be evaluated through studies of postmenopausal women. The androgen-to-estrogen ratio has been shown to be increased in postmenopausal women when compared with premenopausal women.[29] Many studies have reported that the decreased RNFL thickness in the postmenopausal period can be preserved with estrogen replacement therapy.[5,30,31] These results are inconsistent with the results of our study, which reported the neuroprotective effect of androgens. However, in another study, we reported that androgens have neuroprotective effects in postmenopausal women.[32]

Our study is the first to compare retinal thicknesses in TGM and in women with PCOS with that in CW. The strengths of this study are its prospective nature and its compliance with the exclusion criteria in the selection of the partipants. The main limitation of this study is its small sample size.

Conclusions

In this study, the macular, GCC, and RNFL thicknesses in TGM using exogenous testosterone and of women

with PCOS were compared with those in CW. The retinal thickness values were generally higher in TGM, and in both the nasal RNFL area as well as the parafoveal and perifoveal areas the difference was statistically significant. These results show that there may be a relationship between androgens and retinal thickness, and that the influence of sex hormones on the retina may be important in both healthy and glaucomatous eyes.

Authors' Contributions

Conceptualization, methodology, data curation, methodology, and writing—original draft preparation by O.A. Data curation, investigation, and software by E.E.D. Visualization, supervision, reviewing, and editing by F.V. Data curation and validation by A.Ö.B.

Author Disclosure Statement

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Abbreviations Used

ANOVA = analysis of variance
BMI = body mass index
CCT = central corneal thickness
C/D = cup to disc
CW = cisgender women
GCC = ganglion cell complex
IOP = intraocular pressure
MT = macular thickness
PCOS = polycystic ovary syndrome
RNFL = retinal nerve fiber layer
TGM = transgender men